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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,092	02/27/2001	Marcus Keep	30-200P	1549

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EXAMINER	
MOHAMED, ABDEL A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 07/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,092	KEEP ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1 and 2* is/are allowed.

6)☒ Claim(s) *3-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/30/04 has been entered.

ACKNOWLEDGMENT OF AMENDMENT, REMARKS, DECLARATION AND STATUS OF THE CLAIMS

2. The amendment, remarks and declaration filed under 37 C.F.R. § 1.132 on 3/3/04 are acknowledged, entered and considered. In view of Applicant's request claims 1, 3-6, 8 and 10 have been amended and claims 11 and 12 have been added. Claims 1-12 are now pending in the application. The rejections under 35 U.S.C. 112, second paragraph; 35 U.S.C.112, first paragraph; 35 U.S.C. 102(b); and 35 U.S.C. 103(a) over the prior art of record are withdrawn in view of Applicant's amendment, remarks and declaration filed 3/3/04.

CLAIMS REJECTION-35 U.S.C. § 112 2nd PARAGRAPH

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 3 and 6-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 recites the limitation "said patient" in line 7. There is insufficient antecedent basis for this limitation in the claim.

Claim 6 is indefinite and confusing in referring back to a reference (PCT page 5) because referring back or incorporating a reference is not acceptable claim language and as such the claim is incomplete. A claim should be complete, self-contained and incorporation into a claim by express reference to the publication, patent or reference is not permitted and should not be relied on to define the invention (Ex parte Fressola, Bd. Pat. Appl. & Inter., 5/11/93, p. 1608).

The syntax of claim 8 is not clear in the recitation "An article of manufacture comprising packaging material and pharmaceutical agent is therapeutically effective for reducing or preventing neuronal damage and for causing immunosuppression....." because it is not clear which one is therapeutically effective for reducing or preventing neuronal damage and for causing immunosuppression when administered? Is it the packaging material? or the pharmaceutical agent or both. Appropriate clarification is required.

Claim 8 is indefinite in the recitation "a combination of the before said" and "in admixture" because it is unclear as to what the combination or admixture are? Amounts

of the components in the combination or admixture? And which components are combined or admixed with which or with what? Appropriate clarification is required.

Claim 9 is indefinite in the recitation "a compound of the class of cyclosporins" because it is unclear to which/what specific cyclosporin the claim is referring in view of the family of cyclosporins recited on page 2 in the instant specification? Further, the use of "class" is not appropriate for a Markush species. Appropriate correction is required.

Independent claims 11 and 12 are improperly worded Jepson claims (i.e., improvement claims) because Jepson language requires that any independent claim should contain in the following order, (1) a preamble comprising a general description of all the elements or steps of the claimed combination which are conventional or known, (2) a phrase such as "wherein the improvement comprises," and (3) those elements and/or relationship which constitute that portion of the claimed combination which the Applicant considers as the new or improved portion (See 37 CFR 1.75[e]).

CLAIMS REJECTION-35 U.S.C. 112 1st PARAGRAPH.

4. Claims 3-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising a cyclosporin wherein the cyclosporin is cyclosporin A dissolved in dimethy sulfoxide (DMSO) having the concentration of cyclosporin from 0.1% to 90% by weight of the total composition, does not reasonably provide enablement for various methods of administering cyclosporin composition (e.g., parenterally, orally, inhalationally, rectally,

vaginally, dermally, intra and peri-ocularly, etc.,) into cerebrospinal fluid spaces, or into or adjacent to the brain or spinal cord of a patient in the manner claimed in claims 3-6 and 10, wherein the cyclosporin is cyclosporin A, or functional derivatives, metabolites, variants or salts thereof (claim 7), or an article of manufacture comprising packaging material and pharmaceutical agent wherein the pharmaceutical agent can be used for reducing or preventing neuronal damage and for causing immunosuppression and wherein the cyclosporin is selected from the group consisting of cyclosporin A and a compound of the class of cyclosporins (claims 8 and 9), or a method for treating Alzheimer's disease, Parkinson's disease, sclerosis, HIV neuropathy, Guillain-Barre syndrome, neuronal transplantation, neural xenotransplantation, stroke, brain hemorrhage, brain and spine trauma, ionizing radiation, neurotoxicity of vestibulocochlear structures and retinal detachment (claim 11) or a method for inducing systemic immunosuppression in patients with transplantation and autoimmune disease (claim 12). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not adequately teach methods of various mode of administration by using specific pharmaceutical formulation, and there is no objective factual evidence in the specification showing that treatment or activity whatsoever has occurred using the specific therapeutically effective amount of pharmaceutical formulation in the manner claimed. For example, claim 8 claims an article of manufacture comprising packaging material and pharmaceutical agent is therapeutically

effective for reducing or preventing neuronal damage and for causing immunosuppression, but are all the situation/condition the same for each to achieve the therapeutic effect or does or must it differ based on the disease, disease state, route, dose and dosing regimens and severity of the disease and would one skilled in the art have known to modify the same since achieving a therapeutic effect is undefined in the claim except for reducing or preventing neuronal damage and fro causing immunosuppression, and as such, it is unclear what disease is? and how a therapeutic effect is achieved? Thus, one cannot administer specific effective amount of a pharmaceutical composition in all diseases and situations without appropriate testing because there is no indicia for achieving a therapeutic effective.

Therefore, the instant specification does not commensurate with the claimed subject matter in which the cyclosporin-containing pharmaceutical preparation comprising cyclosporin and DMSO is expected to be particularly useful in a vast range of mode of administration of pharmaceutical formulation in all kinds of possible dosages are contemplated and are encompassed as well as wide range of situations of cerebrospinal or vascular applications to treat Alzheimer's disease, Parkinson's disease, sclerosis, HIV neuropathy, Guillain-Barre syndrome, neuronal transplantation, neural xenotransplantation, stroke, brain hemorrhage, brain and spine trauma, ionizing radiation, neurotoxicity of vestibulocochlear structures and retinal detachment or to a method for inducing systemic immunosuppression in patients with transplantation and autoimmune disease. The specification teaches a method of formulating cyclosporin as

injectable solution as exemplified in Example 1, Examples 2-5 recite protocols for treating acute or chronic brain or spinal damage or immunosuppression.

Thus, there is no evidence or data to show that a similar regimen can be used for various methods of administering cyclosporin composition (e.g., parenterally, orally, inhalationally, rectally, vaginally, dermally, intra and peri-ocularly, etc.,) into cerebrospinal fluid spaces, or into or adjacent to the brain or spinal cord of a patient in the manner claimed in claims 3-6 and 10, wherein the cyclosporin is cyclosporin A, or functional derivatives, metabolites, variants or salts thereof (claim 7), or an article of manufacture comprising packaging material and pharmaceutical agent wherein the pharmaceutical agent can be used for reducing or preventing neuronal damage and for causing immunosuppression and wherein the cyclosporin is selected from the group consisting of cyclosporin A and a compound of the class of cyclosporins (claims 8 and 9), or a method for treating Alzheimer's disease, Parkinson's disease, sclerosis, HIV neuropathy, Guillain-Barre syndrome, neuronal transplantation, neural xenotransplantation, stroke, brain hemorrhage, brain and spine trauma, ionizing radiation, neurotoxicity of vestibulocochlear structures and retinal detachment (claim 11) or a method for inducing systemic immunosuppression in patients with transplantation and autoimmune disease (claim 12).

Therefore, in view of the above, and in view of the fact that there is no enablement in the instant specification for the method of various mode of administration by using specific pharmaceutical formulation, and there is no objective factual evidence in the specification showing that treatment or activity whatsoever has occurred using the

specific therapeutically effective amount of pharmaceutical formulation in the manner claimed, particularly for treating Alzheimer's disease, Parkinson's disease sclerosis, HIV neuropathy, stroke, brain and spinal trauma, autoimmune disease, etc., with the various compounds claimed; the Examiner is unable to determine the enablement of the invention as claimed without appropriate data or evidence. Such evidence in the art for treating acute or chronic brain or spinal damage or immunosuppression details the state of the art in this area and establishes that even the disease is very hard to diagnose, let alone to treat and/or prevent. For example, Ezzell (Scientific America, pages 152-153, March 7, 1993) states on page 152, middle column, before last paragraph that doctors can only diagnose Alzheimer's through a process of elimination, ruling out other disorders such as a slight stroke, a brain tumor, or even an adverse drug reaction. A definitive diagnosis must await death and autopsy, when a pathologist can view the telltale "senile plaques" that pock the brains of Alzheimer's victim. Further, Varon et al. (Dev. Neurosci., Vol. 6, pp. 73-100, 1983/1984) discuss the implications of neurotrophic and neurite-promoting factor and their clinical potential in neuronal diseases such as Parkinson, ALS and Alzheimer in which the authors concluded by stating that further clinical progress requires a better understanding of neurobiological bases of nerve regeneration. Furthermore, Cordell et al. (U.S. Patent No. 5,221,607) discuss that the etiology of Alzheimer's disease is unknown and up to date, there are no means available to treat the pathogenesis of Alzheimer's disease and the paucity of understanding concerning the mechanism of amyloid formation in Alzheimer's disease is a major obstacle in the development and design of therapeutic agents that can

intervene in this process (See e.g., Col.1, lines 55-67). Similarly, Nelson et al. (U.S. Patent No. 5,252,463) discuss serious diseases affecting the central nervous system, which referred as neuropathologies such as Alzheimer's disease and Down's syndrome in which the etiology of Alzheimer's disease is unknown (See e.g., column 1). Thus, the prior art clearly show the unpredictable nature and the complexity of the art in regard to treatment of Alzheimer's disease. Therefore, considering the nature of the treatment of Alzheimer's disease by administering an effective amount of the claimed compound and the limited success achieved; one skilled in the art would not accept the instantly claimed invention as obviously valid and correct without demonstration of evidence or data for the following reasons:

In view of the fact that animals and humans are out bred, in view of the lack of disclosure of suitable animal models for a method of treating or reducing or neuronal damage and for causing immunosuppression by administering effective amount of the pharmaceutical agent, in view of the recognized problems in the art regarding effective treatment of diseases affecting the nervous systems (neuropathologies), in view of the fact that it is difficult to regenerate the neurons in the living body and in view of the fact as acknowledged by Applicant on page 1, last paragraph in the instant specification that several analogs of cyclosporins are not immunosuppressants; a reasonable doubt exists as to the enablement of the claimed method of various mode of administrations using a cyclosporin-containing pharmaceutical preparation for cerebrospinal or vascular application comprising cyclosporin and DMSO for the intended purposes of treating various neuronal diseases/conditions as well as immunosuppressions in patients with

transplantations and autoimmune diseases. Thus, the claims are based on pure speculation that the method would be effective since Applicant has not established any *nexus* between the various claimed mode of administrations and their use in the manner claimed.

Therefore, in view of the above, it would include those that have not been shown or taught to be useful or enabled by the disclosed method of making and using the invention. Further, undue experimentation is necessary to determine if and under what conditions, the claimed invention as broadly claimed is enabled, since a vast range of mode of administration by using specific pharmaceutical formulation in a variety of functional derivatives, metabolites, variants or salts of cyclosporin A are contemplated and are encompassed as well as wide range of situations (i.e., to treat various neurological, immunological and vascular diseases/conditions). The results desired appear to be highly dependent on all variables, the relationship of which is not clearly disclosed. Hence, one of ordinary skill in the art would not be able to identify all the compositions/formulations with wide range of administration intended to be effective for the claimed purpose of cerebrospinal or vascular application of the various diseases and situations as encompassed in the claims would be effective and under what conditions.

Further, the first paragraph of 35 U.S.C. 112 requires, *inter alia*, that a patent specification provide sufficient guidance to enable a person skilled in the art to make and use the claimed invention without undue experimentation. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). While patent Applicants are not

directed to disclose every species that falls within a generic claim, id. At 496, 20 USPQ2d at 1445, it is well settled that "the scope of the claims must bear a reasonable correlation to the scope of the enablement provided by the specification". *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Where practice of the full scope of the claims would require experimentation; factors to be considered in determining whether a disclosure would require undue experimentation ..... include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Therefore, applying the *Wands* factors to the facts of this case, one of skill in the art would find that undue amount of experimentation would be required to practice the full scope of the extremely broad claims fro the reasons given above. Hence, in view of the quantity of experimentation necessary, the lack of adequate guidance or working examples or data, and the breadth of the claims, the claims are not commensurate in scope with the enabling disclosure. Accordingly, filing of evidence commensurate with the scope of the claims or amendment of the claims to what is supported by the enabling disclosure is suggested.

CONCLUSION AND FUTURE CORRESPONDENCE

5. Claims 1 and 2 are allowed, claims 3-12 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed number is (571) 272-0955. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached on (571) 272-0925. The appropriate fax phone number for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 305-7401 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

AAMohamed/AAM

July 6, 2004

Jon P. Weber, Ph.D.
Primary Examiner